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Review article: prevention, diagnosis and management of COVID-19 in the IBD patient

Aysha H. Al-Ani[1] | Ralley E. Prentice[1] | Clarissa A. Rentsch[1] | Doug Johnson[2] | Zaid Ardalan[1] | Neel Heerasing[1] | Mayur Garg[1] | Sian Campbell[2] | Joe Sasadeusz[2] | Finlay A. Macrae[1] | Siew C. Ng[3] | David T. Rubin[4] | Britt Christensen[1]

[1]Department of Gastroenterology, The Royal Melbourne Hospital, Melbourne, Vic., Australia

[2]Victorian Infectious Diseases Unit, The Royal Melbourne Hospital, Melbourne, Vic., Australia

[3]Department of Medicine and Therapeutics, Institute of Digestive Disease, State Key Laboratory of Digestive Diseases, Li Ka Shing Institute of Health Science, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China

[4]Inflammatory Bowel Disease Center, University of Chicago Medicine, Chicago, IL, USA

Correspondence
Britt Christensen, The Royal Melbourne Hospital, Gastroenterology Department, 300 Grattan St, Parkville, Vic., Australia.
Email: britt.christensen@mh.org.au

Summary

Background: The current COVID-19 pandemic, caused by SARS-CoV-2, has emerged as a public health emergency. All nations are seriously challenged as the virus spreads rapidly across the globe with no regard for borders. The primary management of IBD involves treating uncontrolled inflammation with most patients requiring immune-based therapies. However, these therapies may weaken the immune system and potentially place IBD patients at increased risk of infections and infectious complications including those from COVID-19.

Aim: To summarise the scale of the COVID-19 pandemic, review unique concerns regarding IBD management and infection risk during the pandemic and assess COVID-19 management options and drug interactions in the IBD population.

Methods: A literature review on IBD, SARS-CoV-2 and COVID-19 was undertaken and relevant literature was summarised and critically examined.

Results: IBD patients do not appear to be more susceptible to SARS-CoV-2 infection and there is no evidence of an association between IBD therapies and increased risk of COVID-19. IBD medication adherence should be encouraged to prevent disease flare but where possible high-dose systemic corticosteroids should be avoided. Patients should exercise social distancing, optimise co-morbidities and be up to date with influenza and pneumococcal vaccines. If a patient develops COVID-19, immune suppressing medications should be withheld until infection resolution and if trial medications for COVID-19 are being considered, potential drug interactions should be checked.

Conclusion: IBD patient management presents a challenge in the current COVID-19 pandemic. The primary focus should remain on keeping bowel inflammation controlled and encouraging medication adherence.

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Aysha H. Al-Ani and Ralley E. Prentice should be considered joint first authors.

1 | INTRODUCTION

In December 2019, reports of a novel coronavirus, since named SARS-CoV-2, emerged from Wuhan, central Hubei Province, China.[1-3] The virus causes the disease COVID-19, which manifests as a severe acute respiratory illness that can be complicated by acute respiratory distress syndrome (ARDS), multiorgan failure and even death.[3] Following rapid spread of the virus across the globe, the World Health Organisation (WHO) declared COVID-19 a pandemic on 11 March 2020.[2] There are currently almost 2 million confirmed cases across more than 200 countries with a total death count greater than 100 000 at the time of writing.[2] As the pandemic expands, there has been increasing concern regarding the impact of COVID-19 on patients with IBD.

The primary management of IBD involves treating uncontrolled inflammation with a significant number of patients requiring immune-based therapies.[4] In the last decade, there has been a considerable expansion of the therapeutic armamentarium for patients with IBD to include immunomodulators, TNF antagonists, non-TNF-targeted biologics and targeted small molecule therapies.[5] However, these therapies, in addition to malnutrition which can complicate IBD, may weaken the immune system and potentially place IBD patients at increased risk of infections and infectious complications.[6]

Consequently, there is a concern that IBD patients are at greater risk of developing COVID-19 and at increased risk of progressing to a more severe clinical course or even death compared to the general population. In addition, if an IBD patient develops COVID-19, there is a lack of guidance on medication management and concern regarding drug interactions if trial medications are utilised to treat COVID-19.

Therefore the aim of this review is to summarise the evidence and discuss in detail the data regarding the risks of developing COVID-19, strategies that can be implemented to reduce these risks and issues surrounding the treatment of COVID-19, including potential drug interactions and IBD medication management, in the IBD patient cohort.

2 | CORONAVIRUSES

Coronaviruses (of the family coronaviridae) are a group of related single-stranded, positive sense, enveloped RNA viruses. They are the largest known RNA viruses, ranging from 26 to32 kilobases in size.[7] They are named after their appearance under electron microscopy, showing crown or halo (solar corona)-like spikes (virions) on their surface. [8] These viruses are capable of causing illness in humans and other mammals as well as birds.

Human coronaviruses (HCoVs) were first discovered in 1960. There are currently seven known human coronaviruses: Human coronavirus 229E (HCoV-229E), Human coronavirus OC43 (HCoV-OC43), Human coronavirus HKU1 (HCoV-HKU1), Human coronavirus NL63 (HCoV-NL63), Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) and Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). [9] These viruses are all known to cause respiratory symptoms ranging broadly in severity, both between the different viruses and in different hosts infected with the same virus. Most spread easily and result in relatively mild illness in immunocompetent patients, with certain strains being responsible for almost 30% of the common cold.[10]

Other coronaviruses (CoVs), including the SARS-CoV and the MERS-CoV, have previously emerged as epidemics with significant mortality and socioeconomic impact. Compared to SARS-CoV-2, MERS-CoV causes a much more severe illness, with a case-fatality rate (CFR) of up to 30%, but appears to have a lower person-to-person transmission, limiting its global impact.[5] There are still new cases of MERS being reported today.[11] Similarly, the SARS-CoV outbreak in 2002-2003 had a high CFR (9.6%), but its reduced infectivity compared with SARS-CoV-2 lessened its overall impact.[12] This outbreak appears to have been contained.[12] SARS-CoV-2 is the first pandemic coronavirus. Therefore, it poses a threat of uncertain dimensions and represents uncharted territory for the public and global healthcare systems alike.[2,3]

3 | SARS-COV-2 VIRUS AND COVID-19

SARS-CoV-2, the virus previously known as novel 2019-coronavirus, causes the disease COVID-19. It was first discovered following the reports of an outbreak of pneumonia in China, with initial infections linked to a single seafood market.[1,13] Genetic studies have shown its genetic sequence is 82% similar to SARS-CoV, and 89% similar to bat-SL-CoVZC45 and bat-SL-CoVZXC21, leading to the postulation that bats served as reservoir host for the new coronavirus' progenitor.[14] Human transmission is thought to have been facilitated by an animal intermediate host, currently hypothesised to be a pangolin.[15]

3.1 | Transmission

Human-to-human transmission is believed to be predominantly via direct contact, exhaled droplets and fomites from an infected individual.[16] SARS-CoV-2 can also be detected in saliva, urine and the gastrointestinal tract in both biopsy specimens and stools, although their role in transmission remains unclear.[17-19] Data suggest it is more easily transmitted than seasonal influenza based on a basic reproduction number (R_0 - the expected number of cases directly generated by one case in the population) of 2-2.5.[20]

Entry of coronaviruses into human target cells requires spike (S) protein binding to a cellular receptor followed by S protein priming by host proteases to facilitate cell entry.[21] SARS-CoV-2 human-to-human transmission is enabled by the interaction of the SARS-CoV-2 S-protein with the human angiotensin-converting enzyme 2 (ACE2) receptor.[17,18] Transmission occurs when the virus enters the nose, mouth or eyes, and potentially the digestive system and attaches to cells that produce ACE2. ACE2 are found in multiple organs and are

highly expressed in lung AT2 cells, enterocytes of the small intestine and colon.[22,23] Once the virus is attached to ACE2 it uses the host serine protease TMPRSS2 for S priming allowing fusion of viral and cellular membranes and viral entry into the cell.[21]

Once a person develops initial symptoms of COVID-19, respiratory viral shedding occurs for a median of 20 days in survivors and is sustained until death in nonsurvivors.[24] Of note, prolonged shedding has been demonstrated with other coronaviruses in immunocompromised patients[25] and in immunocompromised animals with MERS-CoV.[25,26] However, the implications of this prolonged shedding are unknown as virus detected by PCR does not necessarily indicate viable virus or infectivity; a study of nine COVID-19 patients demonstrated that infectious virus was only isolated from samples taken before day 8 of symptom onset despite ongoing high viral loads and shedding after this time point.[27] Asymptomatic people are also potential sources of SARS-CoV-2 as transmission may occur in the pre-clinical period (2-14 days) or from an oligosymptomatic individual.[27,28] Furthermore the virus has been detected in up to 50% of stool specimens and can remain positive for viral RNA following negative respiratory samples in more than 20% of SARS-CoV-2 patients.[19,22,29] These characteristics may have implications regarding isolation and decision-making for IBD patients who are infected with SARS-CoV-2 although there are no evidence-based guidelines on this currently.

3.2 | Symptoms

The major clinical manifestations of COVID-19 are fever (44% on admission and 89% during admission), dry cough (68%), shortness of breath (19%), diarrhoea/vomiting/abdominal pain (20%), generalised myalgia/arthralgia (15%), headache (14%), malaise and bilateral interstitial pneumonia.[15,19,30] COVID-19 pneumonia manifests with chest CT imaging abnormalities, even in asymptomatic patients, with rapid evolution from focal unilateral to diffuse bilateral ground-glass opacities that progress to or co-exist with consolidations within 1-3 weeks. [15]

While the mechanism of COVID-19 induced gastrointestinal symptoms remains to be clarified, enteric symptoms may occur due to malabsorption secondary to direct damage of the invaded enterocyte in the setting of a viral infection.[18] Furthermore, there is a recent case report of a possible SARS-CoV-2 gastrointestinal infection causing acute haemorrhagic colitis and signalling COVID-19 disease.[31] It is not clear if gastrointestinal symptom rates secondary to COVID-19 differ in patients with IBD but if an IBD patients presents with worsening gastrointestinal symptoms, COVID-19 infection should be considered as a differential.

3.3 | Demographics

The median age of an infected individual is 51 years old and the majority of infected individuals range from 30 to 69 years.[16] Fifty-one percent of reported cases is male. Healthcare workers may be at increased risk of infection secondary to close contact with infected patients and exposure to aerosolised virus from medical equipment and procedures including endoscopy.[32] In China healthcare workers made up 3.5% of COVID-19 patients and Italy have reported that 20% of its responding healthcare work force is being infected.[17,33] Current data suggest that children under the age of 18 years have a low infection rate (2.4%), with a large proportion being identified through contact tracing in adults rather than through symptomatology.[16]

3.4 | Disease course

The median incubation period for SARS-CoV-2 is 4-5 days, with most patients having symptom onset before 14 days, but there have been cases with longer incubation.[34] A mean interval of 9.1-12.5 days between illness onset and hospitalisation has been documented highlighting the challenge in the identification and isolation of individuals at an early stage of disease.[35] In recovered cases, the median time from initial symptoms to discharge from hospital was 22 days and in those that succumbed the average time to death was 18.5 days.[35]

Overall CFR of COVID-19 are estimated to be approximately 1%-2%, rising to more than 15% in patients aged 80 years and over.[36] Current WHO data surmise that most cases of COVID-19 have mild to moderate disease (80%) with 13.8% experiencing severe disease defined by the following signs and symptoms within 24-48 hours: shortness of breath; tachypnoea >30 breaths per minute; hypoxia <93%; hypoxaemia with PaO_2/FiO_2 ratio < 300 and/or pulmonary infiltrates >50% of the lung field.[16] Critical infections occur in 6.1% and are exemplified by septic shock, respiratory failure and/or multiorgan failure.[1,16] Approximately one quarter of hospitalised patients require intensive care and 4.3% die.[1] The primary reason for transfer to ICU is the development of organ dysfunction with ARDS being the main catalyst.[1]

3.5 | Risk factors

Risk factors for contracting COVID-19 have not been fully elucidated. Healthcare professionals are at greater risk secondary to increased exposure[32] and it is thought that smoking may exacerbate contraction.[37] For all patients with COVID-19, severity and mortality is associated with age (median age 66 years for critically ill vs 51 years in the overall patient population) and underlying cardiovascular disease, hypertension, chronic pulmonary disease, diabetes and cancer.[16,17,38] Severe COVID-19 is less common in children with reports suggesting approximately 5% develop severe disease and 0.6% become critical.[39] The crude fatality rate is higher in males (4.7%) vs females (2.8%) and smokers.[16,17,35] Risk factors are summarised in Table 1.

Specific risk factors for developing COVID-19 in IBD patients are yet to be determined. For lower respiratory tract infections with

seasonal (non-COVID-19) coronavirus, risk factors in other immunocompromised patient groups have included age >50 years, receipt of corticosteroids, lymphopenia and neutropenia.[26,40] For IBD patients, the greatest risk factor for general immunosuppression and infections remains pharmacological.[41,42] Nutritional status, co-morbidities, age and disease activity also contribute.[42,43] Of these, malnutrition (OR: 6.26 [95% CI: 1.20-32.78])[41,42] and disease activity (OR: 3.35 [95%CI: 1.23-9.23, P = 0.02])[44] are significant nonpharmacological risk factors that are modifiable for infection and therefore nutritional support and medical treatment aiming for disease control should be optimised.[41,42] Furthermore, low vitamin D levels are prevalent in IBD patients and may be associated with an increased risk and/or severity of influenza and COVID-19.[45,46] Vitamin D increases anti-inflammatory cytokines and lowers viral replication, which in turn may reduce pro-inflammatory cytokines that propagate lung injury and ARDS.[45-47] Therefore assessment of vitamin D and supplementation when it is low is reasonable.

As gastrointestinal tract permeability may be increased in IBD patients[18] with higher expression of ACE2 in inflamed bowel,[48] there is also a theoretical increased risk of SARS-CoV-2 infection via the gut in IBD patients. Despite this, there is no current evidence of increased infection rates or worse disease severity of COVID-19 in IBD patients. Indeed, so far, no patient with IBD has been reported to have contracted COVID-19 from the tertiary IBD centres in Wuhan where the virus originated[49] and, despite IBD being a reasonably common condition, very low rates have been described in an international COVID-IBD registry as of 11 April 2020. At time of writing, 457 (270 Crohn's disease [CD]; 185 UC/unspecified) cases of COVID-19 in IBD had been reported with 26% of CD and 36% of ulcerative colitis (UC) patients requiring hospitalisation and 3% of CD and 5% of UC patients requiring ICU. Fifteen deaths have been reported.[50] This appears to be a notable under-representation of COVID-19 infection in IBD patients compared to the prevalence of IBD and COVID-19 separately in the community. As yet, it is unclear if this is secondary to low COVID-19 infection rates or to significant under-reporting of COVID-19 infection in IBD patients.

TABLE 1 Risk factors for being infected with COVID-19 and developing severe complications

Possible risk factors for COVID-19 infection[115-117]
Smoker
Healthcare worker
Nursing-home/community living environment
Possible risk factors for developing severe/critical COVID-19[17,19,116]
Age > 50
Diabetes
Hypertension
Malignancy
COPD
Smoker
Lymphopenia
Neutropenia
Higher LDH and D-dimer levels >1 µg/mL on admission
Post-operative setting
Corticosteroids
?Diarrhoea
Further risk factors for death if admitted to ICU[17,116]
Tachycardia
Lymphopenia
Hypoxia
Coagulopathy

3.6 | Diagnosis

A diagnosis of COVID-19 should be considered in patients who display fever, cough, anosmia, nausea, vomiting and diarrhoea. Of note, a subgroup of patients may present with mild disease marked by the presence of diarrhoea initially and these patients often experience delayed diagnosis compared to those that present with respiratory symptoms.[51] Biochemical markers of COVID-19 include lymphopenia, thrombocytopenia and leukopenia as well as elevated C-reactive protein (CRP), which may also correlate with severe disease. [17] Less commonly, there may also be elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatine kinase (CK) and D-dimer.[17]

Recommendations on whom to test for COVID-19 will vary depending on the local guidelines, availability of testing kits and regional transmission dynamics. In high-risk settings where an outbreak has occurred, all patients with clinical features consistent with COVID-19 should be considered for testing. In non-outbreak areas, a case of COVID-19 should be suspected and tested for if a patient has clinical features suggestive of COVID-19 and fits epidemiologic criteria for example international travel or contact with a confirmed COVID-19 case. A patient is also considered a suspect case of COVID-19 regardless of their history if they are admitted to hospital with acute respiratory illness or unexplained fever.

Diagnosis of COVID-19 is via nucleic acid testing of nasopharyngeal and oropharyngeal swabs.[52] Serology testing is currently not widely available. It is important to ensure that routine local protocols for testing in acute pneumonia/pneumonitis are also followed, such as bacterial cultures, urinary antigen testing, acute and convalescent serology and respiratory virus panels. At this stage, faecal sampling is not standard; however, this may be indicated in those with gastrointestinal symptoms. A positive test for COVID-19 must be immediately notified to the relevant communicable diseases agency.[52]

4 | MANAGEMENT OF IMMUNOSUPPRESSION WITH COVID-19

Despite a lack of evidence demonstrating any increased susceptibility to COVID-19,[50] medications used in the management of IBD

TABLE 2 IBD medications and infection risk

	Risk of respiratory tract infections	Risk of serious infections
Steroids		
Prednisolone	URTI for influenza compared to placebo • OR 1.22 (95% CI, 1.08-1.38)[62] LRTI compared to placebo • OR 3.62 (95% CI 3.30-3.98)[62]	OR 1.92 (95% CI 0.36-10.21) compared to placebo[63]
Budesonide	No increase in adverse events compared with placebo[118]	RR 0.97 (95% CI 0.76-1.13) compared to placebo[118] OR 0.73 (95% CI 0.36-1.50) Budesonide MMX compared to placebo[69] OR 0.94 (95% CI 0.56-1.59) Budesonide compared to placebo[69]
Beclomethasone	No increase in adverse events compared with placebo[119]	OR 0.30 (95% CI 0.01-8.29) compared to placebo[69] OR 3.32 (95% CI 0.13-84.9) compared to prednisolone [69]
Immunomodulators		
Thiopurines	2.1 per patient-years[70]	OR 0.143 (95% CI 0.43-4.76) compared to placebo[70]
Methotrexate	OR 1.02 (95% 0.88-1.19)[73] compared with placebo	OR 0.52 (95% CI 0.04-6.34) compared to placebo[73]
Biologic therapy		
Anti-TNF	URTI • Infliximab: 25% vs 9.8% placebo • Adalimumab: 16.7% vs 14.5% placebo[76] LRTI compared to placebo • OR 1.28 (95% CI: 1.08-1.52)[62]	OR 1.43 (95% CI: 1.11-1.84; $P = 0.006$) compared to placebo[75]
Ustekinumab	URTI • 10.7% in ustekinumab 12-weekly and 12.9% ustekinumab 8-weekly vs 7.5% placebo[82]	4.21 (95% CI 3.25-5.36) in ustekinumab group vs 3.97 (95% CI 2.05-6.97) in placebo per 100 patient-years of follow-up[82]
Vedolizumab	URTI compared to placebo • HR 1.23, log-rank $P = .173$[120] LRTI compared to placebo • HR 0.95, log-rank $P = 0.851$[120]	4.3/100 patient-years (95% CI 3.7-4.9) vs 3.8/100 patient-years (95% CI 1.2-6.4) for placebo [86]
Small molecule therapy		
Tofacitinib 5 mg	URTI • 4.5% sv 3.3% with placebo in RA patients[121] Nasopharyngitis 10% vs 2.8% placebo[122]	2.3 (95% CI: 1.8 to 2.8) /100 patient-years (in RA)[123]
Tofacitinib 10 mg	URTI • 6% vs 4% with placebo in UC patients[122] Nasopharyngitis 14% vs 2.8% placebo[122]	2.7 (95% CI: 2.3 to 3.1)/100 patient-years (in RA)[123]

Abbreviations: HR, hazard ratio; LRTI, lower respiratory tract infection; OR, odds ratio; RA, rheumatoid arthritis; CI, confidence interval; RR, relative risk; URTI, upper respiratory tract infection.

have been shown to increase the risk of respiratory tract infections and serious infections to varying degrees (Table 2). However, theoretically, there may also be some beneficial effects seen with certain immunosuppressive medications, given the cause of death in COVID-19 is a cytokine storm resulting in ARDS.

Overall, apart from corticosteroids, the risks of IBD therapies, particularly 5-ASAs and biologics, appear limited, and the importance of careful discussion regarding the risks versus benefits of medications with patients and among medical practitioners cannot be overstated. Inappropriate cessation of effective agents due to unjustified fear of adverse events may lead to IBD relapse, which when requiring the use of steroids or hospitalisation may inadvertently strain medical resources and increase the risk of COVID-19 exposure and infection.

4.1 | Sulfasalazine and 5-aminosalicylates (5-ASAs)

Sulfasalazine and the 5-ASA medications are used as first-line induction and maintenance treatment for UC. 5-ASAs have very mild immunosuppressive activity and they are often well tolerated with minimal side effects. There are no reports of these medications being associated with an increased risk of infection and studies of large cohorts evaluating the safety profile of 5-ASAs do not demonstrate an increased risk of serious or opportunistic infections.[53]

Sulfasalazine and 5-ASA

- Treatment with 5-ASA therapy should continue without concern for increased risk of contracting or developing severe COVID-19.
- If a patient is in contact with someone who has COVID-19 or develops COVID-19, treatment with 5-ASA should continue.

Sulfasalazine and 5-ASA

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4.2 | Corticosteroids

Corticosteroids systemically reduce inflammation by turning off multiple inflammatory genes. In patients with COVID-19, a systemic inflammatory response syndrome can perpetuate lung injury with persistent inflammation resulting in ongoing pulmonary damage even subsequent to viral suppression.[54] Corticosteroids have therefore been trialled in the treatment of coronavirus', including COVID-19.[54-56] However corticosteroids in these infections have no demonstrated benefit; rather, steroids have been shown to increase harm in the management of SARS,[54] MERS[55] and influenza.[56] In a retrospective observational study of 309 patients who were critically ill with MERS, the 159 patients who received corticosteroids were more likely to require mechanical ventilation, vasopressors and renal replacement therapy.[55] Furthermore, corticosteroids were not associated with a difference in 90-day mortality (adjusted odds ratio 0.8, 95% CI: 0.5-1.1, P = 0.12) but were associated with delayed clearance of viral RNA from respiratory tract secretions (adjusted hazard ratio 0.4, 95% CI 0.2-0.7; P = 0.0005).[55] In SARS, corticosteroid treatment was of no clinical benefit in regard to infection resolution but was associated with an increased risk of psychosis,[57] delayed clearance of viral RNA,[58] diabetes[59] and avascular necrosis.[60] Finally, in a systematic review on corticosteroid treatment in influenza patients, corticosteroids were associated with an increased length of stay in intensive care, an increased rate of secondary bacterial and fungal infections and an increase in mortality compared to those who did not receive corticosteroids.[56] Whether this indicates that those already on steroids for management of other medical illnesses are at increased risk of adverse outcomes with COVID-19 remains uncertain; however, steroids are widely known to increase the risk of opportunistic infections and respiratory infections including influenza, pneumonia and severe infections and are associated with an increased risk of hospitalisation and mortality in IBD patients, particularly at doses of prednisolone or its equivalent ≥20 mg.[61-64] Therefore, due to the possible risks with systemic corticosteroids, IBD patients should taper their systemic corticosteroids to the lowest tolerated dose with complete weaning where possible. Patients should also be advised not to self-commence systemic corticosteroids to control IBD symptoms unless under the direction of their gastroenterologist. Where possible if patients come into contact with a COVID-19 patient or develop COVID-19 symptoms they should also taper corticosteroids.

Data for budesonide and beclomethasone, locally acting corticosteroids with low systemic bioavailability, demonstrate that these medications are associated with significantly fewer side effects when compared to systemic corticosteroids with adverse events similar to placebo.[65-69]

Corticosteroids

- Corticosteroids (particularly ≥20 mg prednisolone or its equivalent) are associated with an increased risk of infection; however, it is unclear if treatment with corticosteroids is associated with an increased risk of COVID-19 infection or complications.
- Where possible, corticosteroid use should be avoided and rapid tapering should be considered ± switch to budesonide. This must be weighed up against the risk of IBD flare.
- If a patient requires a course of corticosteroids to treat a flare, consider the use of budesonide or beclomethasone where possible, and in CD, consider exclusive enteral nutrition (EEN) as an alternative induction agent.
- If a patient is in contact with a person with COVID-19 or develops COVID-19, taper corticosteroids ± switch to budesonide or beclomethasone where possible, but consider need for stress-dose steroids if septic or shocked.

4.3 | Immunomodulators

Immunomodulators are commonly used in the management of IBD, as monotherapy or combination therapy, with a view to maintaining remission in isolation or enhancing the pharmacologic profile of the biologics. These agents, previously used predominantly in the chemotherapy and transplant setting, act to alter immune function by causing apoptosis of T cells, integral in host defence against viral pathogens.[70] Thiopurines (azathioprine and mercaptopurine) have been associated with an increased risk of serious and opportunistic infections[70] and appear to reduce immune response to viruses, with their use being associated with up to a fivefold increased risk of herpes simplex virus lesions and significant worsening of viral warts.[71] However there is limited evidence that they increase the risk of either upper respiratory tract infections or pulmonary infections.[70,71] In addition, mercaptopurine has been shown to inhibit one of the proteases essential to viral maturation of MERS-CoV in vitro, although no further animal-based models exist to suggest clinical efficacy.[72]

Methotrexate has variably been demonstrated to increase the risk of infections in patients with inflammatory diseases. Reassuringly, a recent systematic review reassuringly found that in the nonrheumatoid arthritis inflammatory disease population, there was not an

increased risk of infection with methotrexate (1.03, 95% CI0.82-1.3).[73] This applied similarly to respiratory infections specifically.[74]

Immunomodulators

- No clear evidence of increased risk of lower respiratory tract infections with immunomodulators
- Some evidence that thiopurines impair viral immunity and mixed evidence that that they have some anti-viral activity.
- Weigh risks and benefits, but most patients can continue on stable dose. In older patients, those in sustained remission and with co-morbidities, consider ceasing.
- Avoid commencing thiopurines or increasing dose: this will allow patients to avoid potential side effects and frequent pathology monitoring.
- If a patient is in contact with someone with COVID-19 consider temporarily withholding thiopurines for 2 weeks.
- If a patient tests positive for SARS-CoV-2 and/or develops COVID-19, consider temporarily withholding thiopurines until patient clears infection.

4.4 | Biologics

4.4.1 | TNF antagonists

Anti-TNF agents have been shown to increase the risk of upper and lower respiratory tract infections, as well as serious and opportunistic pulmonary infections.[62,75,76] Compared with anti-TNF monotherapy, risk of serious infections increases with combination of anti-TNF and an immunosuppressive agent or most significantly in combination with corticosteroids.[77] In a study that did not separate mono—or combination—anti-TNF therapies, the risk of pneumonia was only slightly increased in patients receiving a TNF antagonist (OR: 1.28, 95% CI [1.08-1.52]).[62]

Of note, anti-TNF therapy has been employed in the management of severe sepsis, with a meta-analysis demonstrating reduced overall mortality when used in severe sepsis before shock, and improved survival at 30 days in patients with shock or high baseline levels of IL-6.[78] There are no data on the incidence and severity of SARS or COVID-19 in patients on anti-TNF medications. Anti-TNF agents were utilised in the initial phase of the SARs epidemic, although the overall evidence for efficacy is lacking.[79]

4.4.2 | Biologics: non-TNF antagonists

The main non-TNF antagonist biologics for IBD include the anti-IL12/23 biologic ustekinumab and the anti-integrin therapy, vedolizumab. Reassuringly, the risk of severe respiratory tract infections, severe infections in general or opportunistic infections does not appear to be increased in long-term follow-up studies of ustekinumab in both IBD and psoriasis.[80-82] Similar data have also been reported for vedolizumab.[83-86] There is a theoretical concern of an increased risk of respiratory infections, and hence COVID-19, with vedolizumab treatment as vedolizumab binds the T-cell integrin receptor $\alpha_4\beta_7$, inhibiting its binding to MADCAM1 present on the small intestinal endothelium and vasculature. These receptors are also expressed in the T cells occupying the nares, although to a far lesser extent when compared to the intestine.[87] Reassuringly, a recently conducted network meta-analysis failed to demonstrate a significant difference in rates of nasopharyngitis between anti-TNF agents and vedolizumab, and multiple studies on the safety of vedolizumab have demonstrated that there is no increased risk of respiratory, systemic or serious infections in patients on vedolizumab over placebo .[83-86]

Biological therapies

- Biological therapies appear relatively safe.
- If commencing on a new patient, where appropriate consider subcutaneous dosing mechanism to reduce infusion centre burden/health facility contact.
- Elective switching from infliximab infusions to subcutaneous anti-TNF formulations is not advised as this may increase the risk of relapse.[88]
- If on combination therapy and patient is in deep remission and/or older, consider withholding/ceasing immunomodulator therapy to reduce infection risk. If possible utilise therapeutic drug monitoring to guide decision.
- If patient is in contact with someone who has COVID-19, consider withholding anti-TNF therapies for 2 weeks. Likely safe to continue other biologics.
- If patient tests positive for SARS-CoV-2 and/or develops COVID-19, consider withholding biologics until patient clears infection.

4.5 | JAK inhibitors

Tofacitinib, an orally active Janus kinase (JAK) inhibitor, is employed in the management of UC, particularly in those patients with disease refractory to biologic agents. Tofacitinib may impair immunity to viral infections and has been shown to increase the risk of herpes zoster (HZ) infection, with 5.6% of UC patients developing HZ on long-term extension trials.[89] However, long-term follow-up of patients treated with this agent for rheumatoid arthritis have described rates of URTI (18.8%) and nasopharyngitis (14.6%) comparable to that of anti-TNFs.[90] Serious infection was found to be increased with tofacitinib in the induction trials for UC, but similar across treatment groups including placebo in the maintenance trial.[91] Of 4789 patients treated with

tofacitinib in phase II, III and LTE studies, 259 patients had serious infections (3.09 events per 100 PY [95% CI 2.73, 3.49]), and the most common infection was pneumonia.[92] Higher doses of 10 mg twice daily as opposed to 5 mg twice daily, age >65 years, corticosteroids >7.5 mg/d and diabetes were also independent factors associated with increased serious infection risk.[92,93] Therefore, patients on tofacitinib should be maintained on the lower 5 mg twice daily dose compared to 10 mg twice daily where possible and weaned off corticosteroids.

Interestingly, baricitinib, a JAK inhibitor used in rheumatoid arthritis, has a potential therapeutic role in the management of SARS-CoV-2 through both its anti-inflammatory action and Numb-associated kinase (NAK) inhibition. Tofacitinib has no affinity for this particular kinase. NAKs are involved in the function of clathrin, which mediates endocytosis of SARS-CoV-2 into cells resulting in infection.[94] Due to the anti-inflammatory effects of the JAK inhibitors, it has also been speculated that they may be able to combat the elevated levels of cytokines observed in COVID-19 which may potentially further decrease the severity of the infection.[94]

JAK inhibitors

- JAK inhibitors may impair viral immunity.
- Use lowest effective dose to maintain remission: Where possible maintain patients on 5 mg twice daily as opposed to 10 mg twice daily.
- Avoid commencing tofacitinib during pandemic unless there are no other alternatives. This will allow patients to avoid potential side effects and frequent pathology monitoring.
- If a patient is in contact with someone with COVID-19, consider temporarily withholding tofacitinib for 2 weeks.
- If a patient tests positive for SARS-CoV-2 and/or develops COVID-19, consider withholding tofacitinib until patient clears the infection.

4.6 | Recommencement of medications following COVID-19 infection

If a patient is exposed to or gets infected with COVID-19, the withholding of immunosuppressive medications should be considered where possible. Patients exposed to COVID-19 will usually display symptoms of COVID-19 within 14 days and therefore if they remain asymptomatic, recommencement of these medications can occur at this time point. If a patient develops COVID-19 and has held/delayed their IBD medication, recommencement of medication can occur once the infection has been cleared.

To clear a patient of COVID-19:

1. Where testing is available: patients can be cleared of COVID-19 if they have clinically recovered and have two negative nasopharyngeal swabs at 24 hour intervals at least 8 days after symptom onset.[95]
2. Where testing capacity is limited: due to potential prolonged shedding, guidelines suggest an immunocompromised patient should wait at LEAST 14 days after symptom onset (as opposed to 8 days in non-immunocompromised patients) and be cleared if there is clinical improvement in symptoms and complete resolution of fever for at LEAST 3 days.[95]

It is important to note that many IBD medications may take months to be eliminated from the body so the utility of withholding these medications in the short term is likely to be limited. (See Table 3).

5 | NONPHARMACOLOGICAL RECOMMENDATIONS

The response to COVID-19 is rapidly evolving and gastroenterologists should regularly review local, institutional and international recommendations. Despite limited data, patients with IBD are theoretically at increased risk of COVID-19 due to proximity to medical facilities and immunosuppression. There are therefore several recommendations that clinics and patients can implement to reduce risks.

1. *Optimise health and treat malnutrition:* Nutrition should be optimised as malnutrition can disrupt the innate immune response, including complement and mucosal secretory antibody formation, and is associated with increased infection risk in IBD patients.[96] Smoking has been associated with worse outcomes and increased mortality in COVID-19[17] and therefore patients should be encouraged to quit smoking.
2. *Immunisation:* Immunisation of patients should be strongly encouraged to reduce preventable co-infection with other viruses: Patients should receive pneumococcus (PCV13 and PPSV 23) and influenza (quadrivalent inactivated vaccine) vaccination.
3. *Reduce transmission:* SARS-CoV-2 undergoes human-to-human transmission and strategies to reduce transmission should be instigated in populations at risk.[28] Patients should wash hands with soap and water for 20 seconds or use an alcohol rub, practice social distancing by working from home, standing 2 m apart from people, avoid touching nose, eyes and mouth and avoiding non-essential travel. [97,98]
4. *Avoid healthcare facilities:* A large proportion of healthcare workers have been infected with SARS-CoV-2. Hence, it must be anticipated that super spreading within hospitals may occur.[28] Therefore, patients should preferably avoid hospitals and medical facilities. Suitable patients should have appointments via telehealth allowing for reduced exposure of patients and staff alike to COVID-19.[99] Doctors should attempt to limit non-urgent pathology requests and avoid commencing thiopurines or tofacitinib that require frequent blood monitoring early on. Finally, elective surgery and endoscopy should be postponed. Only urgent endoscopic procedures should occur and if patients require a procedure

TABLE 3 Half-life elimination of IBD medications

Drug	Half-life and time to reach therapeutic effect	Elimination half-life (Most drugs considered to have negligible effect after four-to-five half-lives)	How long the immunosuppression lasts 50% drug eliminated after one elimination half-lives 75% drug eliminated after two elimination half-lives 99% drug eliminated after seven elimination half-lives
Thiopurines (Azathioprine and Mercaptopurine)	$t_{1/2}$:6-TGN and 6-MMP in RBC = 5 days[124] Steady state: 6-TGN and 6-MMP = 4 weeks in RBC[124] Median time to clinical response: 4.5 months[125]	6-TGN in RBC: 6.8 days [IQR 5.9-8.4 days][126a]	75% of 6-TGN eliminated after 10-14 days and expected to be negligible by day 40.[126] Immune reconstitution occurs quickly after thiopurine cessation, if the antigen was not encountered whilst on the thiopurine therapy.[126]
Adalimumab	The subcutaneous injection has a bioavailability of 64% and peak drug concentration at day 5 following injection[127]	17.8-23.9 days (in RA population)[128] Clearance of 0.33L/day[13]	75% eliminated after approximately 40 days
Infliximab	IV infusion 8-9.5 days	7-12 days [129,130]	75% eliminated after 2-3 weeks Low volume of distribution (3-6L/kg) and very low systemic clearance of 11-15ml/hr, mean infliximab is predominantly in the intravascular space for 12-17 days prior to elimination[129,130] Low albumin and higher body weight will speed up elimination[131]
Tofacitinib	3-3.8 hours	3 hours	After a single dose, 95% is expected to be eliminated within 24 hours. Pharmacodynamic effects generally reversible in 14 days after discontinuation
Methotrexate	Methotrexate in serum has a half-life of 6 hours but is converted quickly to methotrexate polyglutamate which is stored for much longer in liver and erythrocytes.[132]	3-10 hours (for methotrexate, not activity)	75% of methotrexate eliminated by within 24 hours but effect continues through active metabolites.
Ustekinumab	First dose given IV to reach peak concentration	19 days	Eliminated at 0.19 L/day (IBD) 75% eliminated by 38 days
Golimumab	2-2.3 days (RA Populations) [128]	14 days	Clearance 7.6 mL/kg/kg 75% eliminated by approx. 30 days
Vedolizumab	Although given intravenously, clinical effect can takes weeks	25 days	Cleared at 0.157 L/day 75% eliminated by 50 days

[a]Low numbers, n = 9 with missing data.[126]

they should have prior screening for COVID-19 if symptomatic. In addition, to limit pharmacy visits and travel on public transport, prescriptions can be changed to a 3-month supply or patients can arrange to have medications delivered by post depending on what is available in their local area.

5. *Infusion centre management:* To reduce the risk of transmission within the infusion centre, patients who are presenting for infusions should be contacted 1-2 days prior to determine their risk of COVID-19. This should include screening for COVID-19 symptoms, confirming no direct contact with a confirmed COVID-19 case and asking about flu-like symptoms. If they have any risk factor, the infusion should be delayed. On attendance, patients should be re-screened for symptoms and have their temperature checked. Alternate entry points for infusion patients to avoid contact with hospitalised patients should be arranged or where possible the infusion centre can be moved to a 'clean' COVID-19 free area. In addition, social distancing between patients chairs should occur and a single nurse per patient arranged to prevent infection spread. Finally, where possible, infliximab infusions should be converted to a 30-minute protocol where safe to do so to limit the duration patients are in the infusion centre.[100]

6 | PHARMACOLOGICAL MANAGEMENT OF COVID-19 IN THE IBD PATIENT

Although there does not appear to be an increased risk of COVID-19 in patients with IBD, when an IBD patient does develop COVID-19,

TABLE 4A COVID-19 experimental treatments

COVID-19 treatments	Trials	Interaction potential
Remdesivir (GS-5734) Adults ≥40 kg: Daily IV dose over 30 min. Day 1: 200 mg Day 2-10: 100 mg Paed <40 kg: Daily IV dose over 30 min. Day 1: 5 mg/kg Day 2-10: 2.5 mg/kg	ClinicalTrials.gov Identifier: NCT04292730 NCT04302766 NCT04292899	Substrate of: CYP2C8, CYP2D6, CYP3A4, transporters OATP1B1 and Pgp - ***Drugs that are strong inducers will decrease remdesivir effect*** Inhibits: CYP3A4, OATP1B1/3, BSEP, MRP4 and NTCP - *unlikely clinically significant* Induces: CYP1A2 and CYP2B6 - *unlikely clinically significant* *All in vitro data*
Lopinavir/ Ritonavir (Kaltera) (400 mg/100 mg) 400mg/100mg twice daily for 14 days   Crushing tablet ↓ absorption ≅ 45%[133]. Use oral liquid (42.4% alcohol and 15.3% propylene glycol) Use compatible feeding tubes (PVC or silicone) Avoid metronidazole and disulfiram Absorbed in jejunum: NG ok; NJ may ↓ effect	ClinicalTrials.gov Identifier: NCT04276688 Chinese Clinical Trials Registry ID: ChiCTR2000029539 EU Clinical Trials Register ID: 2020-000936-23	**Ritonavir/lopinavir:** Lopinovir extensively metabolised by CYP3A Inhibitor of: CYP3A4 (potent*), P-gp, BCPR, OATP1B1 - ***can increase concentration of drugs metabolised or substrates of these pathways*** Inducer of: CYP2C9, CYP2C19, glucuronidation Can prolong PR interval. Rare reports of 2nd and 3rd degree atrioventricular block in patients with underlying risk factors
Chloroquine/Hydroxychloroquine 200 mg three times a day for 10 days 	ClinicalTrials.gov Identifier: NCT04261517 Chinese Clinical Trials Registry ID: ChiCTR2000029609	Metabolised by: CYP2C8, CYP3A4, CYP2D6 Inhibited by: CYP2D6 and P-gp Can prolong QTc interval, consider ECG monitoring where appropriate
Interferon beta	ClinicalTrials.gov Identifier: NCT04276688	Interferons have been reported to reduce CYP450 drug metabolism - care with narrow therapeutic index drugs dependent on CYP450 clearance
Ribavirin  Do not crush –known teratogen. Contact hospital pharmacy for solution compounded from capsules or (SAS) product availability	ClinicalTrials.gov Identifier: NCT04276688	Not metabolised by CYP450 unlikely to contribute to CYP interactions. Inhibits inosine monophosphate dehydrogenase: Can interfere with azathioprine metabolism possibly leading to accumulation of 6-methylthioinosine monophosphate (6-MTIMP), which has been associated with myelotoxicity
Favipiravir 	Chinese Clinical Trials Registry ID: ChiCTR2000029600 favipiravir plus interferon-α ChiCTR2000029544 favipiravir plus baloxavir marboxil	Metabolised by: Nicotinamide adenine dinucleotide phosphate (NADPH) independent and dependent enzymes. Inhibits: CYP2C8 *(strong)* OAT1, OAT3 (mod) CYP1A2*(weak)*, CYP2C9*(weak)*, CYP2C19*(weak)*, CYP2CD6*(weak)*, CYP2E1*(weak)*, CYP3A4*(weak)* Low risk QT prolongation
Atazanavir  Requires pH <4. Avoid antacids 2 h before and 1 hour after. Food ↑ bioavailability Absorbed in jejunum: NG ok; NJ may ↓ effect		Metabolised by: CYP3A4 (extensively) Inhibits: CYP3A4, UGT1A1, OATP1B1 (strong), CYP2C8 (weak) Absorption depends on low pH; drugs increasing pH will decrease atazanavir concentration Dose related prolongation in PR interval. Care with drugs increasing QT interval or in patients with pre-existing risk factors.

(Continues)

TABLE 4A (Continued)

COVID-19 treatments	Trials	Interaction potential
Nitazoxanide (prodrug) **(active metabolite: tizoxanide)** **May be dispersible or crushed– check brand** Take with food - increases bioavailability by 50%.		Nil effects on CYP450 enzymes Tizoxanide highly protein bound (>99.9%) - will compete for binding sites; monitor drugs highly protein bound with a narrow therapeutic index (ie warfarin)
Tocilizumab (IL-6 monoclonal antibody)	ClinicalTrials.gov Identifier: NCT04310228 NCT04306705	Nil significant drug interactions. COVID-19 increases IL-6 expression. Tocilizumab reduces IL-6 expression. IL-6 increases CYP3A4, CYP26C19, CYP2C9, CYP1A2. When tocilizumab is used to treat COVID-19, the effect on drugs effected by these CYP enzymes is unknown.

 Can be crushed;  Can open capsule;  Do not crush;  Liquid product available.

there are no therapeutic options approved for the treatment of coronaviruses. Management of COVID-19 predominantly focuses on supportive care and treating secondary complications.

The highly pathogenic nature of COVID-19 and the need to reduce burden on the health care systems worldwide has encouraged clinicians to examine all possible treatment options. WHO has created a master protocol for a multicentre, adaptive, randomised, double blind placebo controlled trial of the safety and efficacy of investigative therapies for the treatment of COVID-19.[101] There are many drug trials currently occurring. Evidence behind some of these trials is discussed and possible drug interactions with IBD medications and the most commonly cited experimental COVID-19 therapies are summarised in Table 4. Where interactions exist, it is possible for patients to cease their IBD medications and continue on trial medications.

6.1 | Remdesivir (GS-5734)

Remdesivir is a prodrug of the adenosine nucleotide analogue GS-441524 that incorporates into nascent viral RNA chains, inhibiting virus infection in a human cell line (human liver cancer Huh 7 cells).[102,103] It appears to be effective against RNA viruses SARS, MERS and Ebola.[103] In MERS-CoV mouse models, it has been found to reduce the virus titre and improve lung tissue damage.[104] There are currently multiple phase III studies of remdesivir in COVID-19 patients.

6.2 | Lopinavir/ritonavir (Kaltera; 400mg/100mg)

Lopinavir/ritonavir combines two protease inhibitors, the latter used to pharmacokinetically 'boost' lopinavir concentrations and prolong the effect through CYP3A4 inhibition.[104] Licensed as an HIV treatment, in vitro and animal model use in SARS and MERS-CoV resulted in a lower risk of ARDS, lower viral load in lung and extrapulmonary tissue and reduced mortality.[104-106] Results from a recent human trial in China did not demonstrate a statistically significant improvement in time to discharge or clinical improvement. However, treatment was commenced late in the diseases course and only in patients who had developed very severe disease.[107] Further trials are needed to determine the utility of this medication regime. Importantly lopinavir/ritonavir inhibits the metabolism of corticosteroids, tacrolimus, ciclosporin and tofacitinib which may lead to toxicity (Table 4).

6.3 | Chloroquine or hydroxychloroquine

Chloroquine is a widely used anti-malarial and autoimmune disease drug. It has a broad spectrum anti-viral action that is exerted on SARS-CoV by inhibiting the pre-entry point of the viral cycle by interfering with viral binding to cell surface, increasing endosomal pH required for virus/cell fusion and interfering with the glycosylation of cell surface receptors (ACE 2).[108] It also has immunomodulator properties against many cytokines (IL-1b, IL-1, IL-6, IL-12, TNF-a, INF-a, IFNb, IFNy,) which may enhance its anti-viral effect and reduce COVID-19 complications synergistically.[108]

Compared to controls, chloroquine had a superior effect in 100 patients in China infected with COVID-19 in terms of a reduction in exacerbation of pneumonia, duration of symptoms and delay in viral clearance.[109] Chloroquine is not accessible in Australia and it has been suggested that hydroxychloroquine could be an effective alternative given that it is an identical molecule to chloroquine apart from the addition of a hydroxyl group. [108,110] In a French study, 20 COVID-19 positive patients (>12 years of age) received hydroxychloroquine 200 mg three times a day for 10 days after a mean of 4 ± 2.6 days from the onset of symptoms. At day 6, virological clearance was 57% in those receiving hydroxychloroquine compared with 12.5% in the control group (P = .001). In those who also received azithromycin, virological clearance was 100%.[111] A limitation of this study was the exclusion of patients who discontinued treatment, including three patients who were transferred to ICU. Furthermore, the combination of azithromycin and hydroxychloroquine should be considered with caution given additive potential of QT prolongation. More evidence is required before this treatment can be recommended.

TABLE 4B Interactions with IBD medications

COVID-19 treatments	Interactions with IBD treatments							
	Corticosteroids Methylprednisolone, Prednisolone, Budesonide, Beclomethasone, Hydrocortisone*#: Metabolised by CYP3A4, CYP3A5*, CYP3A7* Substrate: P-glycoprotein #Not clinically relevant	**Thiopurines** (azathioprine/ mercaptopurine) Metabolised by: TMPT, HGPRT, XO	**Methotrexate** Transported into the cell by: Reduced folate carrier 1	**Tacrolimus** Inhibits: CYP3A4 (weak) Metabolised by CYP3A4	**Ciclosporin** Metabolised by CYP3A4 Inhibits: CYP3A4 (moderate), P-glycoprotein	**Tofacitinib** Metabolised by CYP3A4 (major) CYP2C19 (minor)	**5ASA**	**Biologics** Adalimumab Infliximab Golimumab Vedolizumab Ustekinumab
Remdesivir (GS-5734) Adults ≥40 kg: Daily IV dose over 30 min. Day 1: 200 mg Day 2-10: 100 mg Paed <40 kg: Daily IV dose over 30min. Day 1: 5 mg/kg Day 2-10: 2.5 mg/kg	🟢	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lopinavir/ Ritonavir (Kaltera) (400 mg/100 mg) 400 mg/100 mg twice daily for 14 days   Crushing tablet ↓ absorption ≅ 45%[133]. Use oral liquid (42.4% alcohol and 15.3% propylene glycol) Use compatible feeding tubes (PVC or silicone) Avoid metronidazole and disulfiram Absorbed in jejunum: NG ok; NJ may ↓ effect	🔺 ↑ **Methylprednisolone:** Consider 50% dose reduction [124]. ↑ **Prednisolone:** ↓ plasma cortisol (level if appropriate) ↑ **Budesonide:** 10-20% absorbed[134]. AUC may ↑ 6.5 fold [24] Consider changing steroid agent or taking budesonide an hour before lopinavir/ ritonavir[124] ↑**Beclomethasone:** Despite low bioavailability, increased absorption may occur, monitor for effect[69]	🟢	🟢	🔺 ↑ Tacrolimus levels: perform levels, consider clinical need and cease ↑ QT prolongation risk– consider baseline and follow up ECG	🔺 ↑ Ciclosporin levels: monitor levels, consider clinical need and dose reduction	🛑 ↑Tofacitinib consider clinical need and cease. If necessary, use lowest dose tofacitinib possible	🟢	🟢

(Continues)

TABLE 4B (Continued)

COVID-19 treatments	Interactions with IBD treatments Corticosteroids Methylprednisolone, Prednisolone, Budesonide, Beclomethasone, Hydrocortisone*#: Metabolised by CYP3A4, CYP3A5*, CYP3A7* Substrate: P-glycoprotein #Not clinically relevant	Thiopurines (azathioprine/ mercaptopurine) Metabolised by: TMPT, HGPRT, XO	Methotrexate Transported into the cell by: Reduced folate carrier 1	Tacrolimus Inhibits: CYP3A4 (weak) Metabolised by CYP3A4	Ciclosporin Metabolised by CYP3A4 Inhibits: CYP3A4 (moderate),P-glycoprotein	Tofacitinib Metabolised by CYP3A4 (major) CYP2C19 (minor)	5ASA	Biologics Adalimumab Infliximab Golimumab Vedolizumab Ustekinumab
Chloroquine / Hydroxychloroquine 200 mg three times a day for 10 days	●	▲ ↑ myelosuppression risk. Recommend ceasing thiopurine in acute severe infection	▲ ↑ myelosuppression risk. Recommend ceasing methotrexate in acute severe infection	▲ ↑ risk of QT-interval prolongation. consider baseline and follow up ECG	▲ ↑ ciclosporin levels, perform levels if appropriate	▲ May ↑ tofacitinib, clinical significance unknown.	●	●
Interferon beta	▲ May ↑ corticosteroid levels, clinical significance unknown, monitor.	●	●	●	▲ May ↑ ciclosporin levels, clinical significance unknown, monitor levels	▲ May ↑ tofacitinib, clinical significance unknown, monitor. Consider lower dose where appropriate	●	●
Ribavirin Do not crush –known teratogen. Contact hospital pharmacy for solution compounded from capsules or (SAS) product availability	●	⬢ ↑ risk of thiopurine induced myelosuppression Cease thiopurine	⬢ ↑ risk myelosuppression Cease methotrexate	●	●	●	●	●
Favipiravir	●	●	●	●	●	●	●	●

(Continues)

TABLE 4B (Continued)

COVID-19 treatments	Interactions with IBD treatments Corticosteroids Methylprednisolone, Prednisolone, Budesonide, Beclomethasone, Hydrocortisone*#: Metabolised by CYP3A4, CYP3A5*, CYP3A7* Substrate: P-glycoprotein #Not clinically relevant	Thiopurines (azathioprine/ mercaptopurine) Metabolised by: TMPT, HGPRT, XO	Methotrexate Transported into the cell by: Reduced folate carrier 1	Tacrolimus Inhibits: CYP3A4 (weak) Metabolised by CYP3A4	Ciclosporin Metabolised by CYP3A4 Inhibits: CYP3A4 (moderate), P-glycoprotein	Tofacitinib Metabolised by CYP3A4 (major) CYP2C19 (minor)	5ASA	Biologics Adalimumab Infliximab Golimumab Vedolizumab Ustekinumab
Atazanavir Requires pH <4. Avoid antacids 2 hours before and 1 hour after. Food ↑ bioavailability Absorbed in jejunum: NG ok; NJ may ↓ effect	↑ **Methylprednisolone:** Consider 50% dose reduction [124]. ↑ **Prednisolone:** ↓ plasma cortisol (level if appropriate) ↑ **Budesonide:** 10-20% absorbed[134]. AUC may ↑ 6.5 fold [24] Consider changing steroid agent or taking budesonide an hour before lopinavir/ ritonavir[124] ↑**Beclomethasone:** Despite low bioavailability, increased absorption may occur, monitor for effect[69]				↑ ciclosporin and ↑ atazanavir. Do not co-administer.	↑ tofacitinib, recommend ceasing tofacitinib		
Nitazoxanide (prodrug) (active metabolite: tizoxanide) **May be dispersible or crushed– check brand** Take with food - increases bioavailability by 50%.								
Tocilizumab (IL-6 monoclonal antibody)								

Can be crushed; Can open capsule; Do not crush; Liquid product available; No clinically significant interaction expected; Interaction, monitor and dose adjust as required;

Do not administer due to interaction and clinical setting

6.4 | Favipiravir (T-705)

Favipiravir, a guanine analogue, effectively inhibits the RNA-dependent polymerase of RNA viruses. This anti-viral effect has efficacy on influenza (approved use), Ebola, yellow fever, chikungunya, norovirus and enterovirus. Activity against COVID-19 has been reported.[112] It is currently being tested in Japan and has no significant drug interactions. In a recent study it has been reported to improve clinical recovery rates at day 7 when compared to arbidol, a flu medication (71% vs. 56%) but there was no difference in auxiliary oxygen or non-invasive ventilation requirements.[113]

6.5 | Alternative therapies

Finally, of note as of 12 March 2020, 379 trials for COVID-19 had been listed on the Chinese Clinical trials Registry; by 15 March 2020 this increased to 420.[114] (Table S1). Of these trials, 122 (29%) involved the examination of Chinese medicines for the treatment of COVID-19. As clinicians we need to be aware of the information available to patients seeking 'natural' alternative therapies and in the absence of clinical evidence, care should be taken when making such suggestions to alleviate panic and inappropriate prescribing.

7 | SUMMARY

IBD patients present a unique challenge in the setting of the current COVID-19 pandemic. Of concern is that, at least theoretically, many medications used to treat IBD may result in a degree of immunosuppression and this may lead to an increased risk of infection with SARS-CoV-2 and complications arising from COVID-19. Despite this, global registries and reports are reassuring and there does not appear to be a signal that IBD patients are at greater risk or severe COVID-19 compared to the general population. These guidelines summarise the treatment approach to IBD patients in the current climate and emphasises the importance of avoiding corticosteroids and maintaining remission by encouraging compliance with patients' usual maintenance medications. If an IBD patient does develop COVID-19, immunosuppressive medications should be withheld where possible until infection resolution and if a medication trial is being considered and patients remain on IBD medications, interactions with current IBD medications should be evaluated.

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AUTHORSHIP

Guarantor of the article: Britt Christensen.

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All the authors approved the final version of the manuscript.

ORCID

Zaid Ardalan https://orcid.org/0000-0001-6952-0985
Neel Heerasing https://orcid.org/0000-0003-0579-2062
Mayur Garg https://orcid.org/0000-0002-9149-3589
Siew C. Ng https://orcid.org/0000-0002-6850-4454
David T. Rubin https://orcid.org/0000-0001-5647-1723
Britt Christensen https://orcid.org/0000-0002-8746-4275

REFERENCES

1. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020.

2. World Health Organisation. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. March 16, 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19--11-march-2020.
3. Chan J-W, To K-W, Tse H, et al. Interspecies transmission and emergence of novel viruses: lessons from bats and birds. *Trends Microbiol*. 2013;21:544–555.
4. Ghosh N, Premchand P. A UK cost of care model for inflammatory bowel disease. *Frontline Gastroenterol*. 2015;6:169–174.
5. Jeong DY, Kim S, Son MJ, et al. Induction and maintenance treatment of inflammatory bowel disease: a comprehensive review. *Autoimmun Rev*. 2019;18:439–454.
6. Rahier JF, Magro F, Abreu C, et al. Second European evidence-based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis*. 2014;8:443–468.
7. Weiss SR, Navas-Martin S. Coronavirus pathogenesis and the emerging pathogen severe acute respiratory syndrome coronavirus. *Microbiol Mol Biol Rev*. 2005;69:635–664.
8. Lai MM, Cavanagh D. The molecular biology of coronaviruses. *Adv Virus Res*. 1997;48:1–100.
9. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol*. 2016;24(6):490–502.
10. Monto AS. Medical reviews. Coronaviruses. *Yale J Biol Med*. 1974;47:234–251.
11. Centres for Disease Control and Prevention. Middle East Respiratory Syndrome (MERS). 2016 Updated August 2, 2019. https://www.cdc.gov/sars/index.html
12. Centres for Disease Control and Prevention. Severe Acute Respiratory Syndrome (SARS). https://www.cdc.gov/sars/index.html. Accessed 15 March, 2020.
13. Lu H, Stratton CW, Tang YW. Outbreak of pneumonia of unknown etiology in Wuhan, China: the mystery and the miracle. *J Med Virol*. 2020;92:401–402.
14. Chan J-W, Kok K-H, Zhu Z, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect*. 2020;9:221–236.
15. Zhang T, Wu Q, Zhang Z. Probable pangolin origin of SARS-CoV-2 associated with the COVID-19 outbreak. *Curr Biol*. 2020.
16. World Health Organisation. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19). March 16, 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
17. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020.
18. Gu J, Han B, Wang J. COVID-19: Gastrointestinal manifestations and potential fecal-oral transmission. *Gastroenterology*. 2020.
19. Tian Y, Rong L, Nian W, He Y. Review article: gastrointestinal features in COVID-19 and the possibility of faecal transmission. *Aliment Pharmacol Ther*. 2020;51:843–851.
20. Zhang S, Diao MengYuan, Yu W, et al. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: a data-driven analysis. *Int J Infect Dis*. 2020;93:201–204.
21. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020.
22. Zhang HKZ, Gong H, Xu D, Wang J, Li Z, Cui X, Xiao J, Meng T, Zhou W, Liu J, Xu H.The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. https://www.biorxiv.org/content/10.1101/2020.01.30.927806v1. March 16, 2020.
23. Garg M, Royce SG, Tikellis C, et al. Imbalance of the renin-angiotensin system may contribute to inflammation and fibrosis in IBD: a novel therapeutic target? *Gut*. 2019.
24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
25. Prescott J, Falzarano D, de Wit E, et al. Pathogenicity and viral shedding of MERS-CoV in immunocompromised rhesus macaques. *Front Immunol*. 2018;9:205.
26. Eichenberger EM, Soave R, Zappetti D, et al. Incidence, significance, and persistence of human coronavirus infection in hematopoietic stem cell transplant recipients. *Bone Marrow Transplant*. 2019;54(7):1058–1066.
27. Wölfel R, Corman VM, Guggemos W, et al. Virological assessment of hospitalized patients with COVID-2019. *Nature*. 2020.
28. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV infection from an asymptomatic contact in Germany. *N Engl J Med*. 2020;382:970–971.
29. Xiao F, Tang M, Zheng X, et al. Evidence for gastrointestinal infection of SARS-CoV-2. *Gastroenterology*. 2020;158:1831–1833.
30. Pan L, Mu M, Yang P, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China. *Am J Gastroenterol*. 2020;115:766–773 (In Press).
31. Carvalho A, Alqusairi R, Adams A, et al. SARS-CoV-2 gastrointestinal infection causing hemorrhagic colitis: implications for detection and transmission of COVID-19 disease. *Am J Gastroenterol*. 2020;In Press.
32. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. *N Engl J Med*. 2020.
33. The Lancet. COVID-19: protecting health-care workers. *Lancet*. 2020;395:922.
34. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. *Ann Intern Med*. 2020;172:577.
35. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020.
36. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese center for disease control and prevention. *JAMA*. 2020.
37. Brake SJ, Barnsley K, Lu W, et al. Smoking upregulates angiotensin-converting enzyme-2 receptor: a potential adhesion site for novel coronavirus SARS-CoV-2 (Covid-19). *J Clin Med*. 2020;9:841.
38. Chan J-W, Yuan S, Kok K-H, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020;395:514–523.
39. Dong Y, Mo XI, Hu Y, et al. Epidemiology of COVID-19 among children in China. *Pediatrics*. 2020.
40. Hakki M, Rattray RM, Press RD. The clinical impact of coronavirus infection in patients with hematologic malignancies and hematopoietic stem cell transplant recipients. *J Clin Virol*. 2015;68:1–5.
41. Toruner M, Loftus EV, Harmsen WS, et al. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology*. 2008;134:929–936.
42. Tosca J, Garcia N, Pascual I, et al. Clinical assessment of risk factors for infection in inflammatory bowel disease patients. *Int J Colorectal Dis*. 2020;35:491–500.
43. Aberra FN, Lichtenstein GR. Methods to avoid infections in patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2005;11:685–695.

44. Wisniewski A, Kirchgesner J, Seksik P, et al. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterology Journal*. 2019;2050640619889763.
45. Grant WB, Lahore H, McDonnell SL, et al. Evidence that vitamin D supplementation could reduce risk of influenza and COVID-19 infections and deaths. *Nutrients*. 2020;12:988.
46. Panarese A, Shahini E. Letter: Covid-19, and vitamin D. *Aliment Pharmacol Ther*. 2020;51:993–995.
47. Tian Y, Rong L. Letter: Covid-19 and vitamin D-authors' reply. *Aliment Pharmacol Ther*. 2020;51:995–996.
48. Ning LongGui, Shan G, Sun Z, et al. Quantitative proteomic analysis reveals the deregulation of nicotinamide adenine dinucleotide metabolism and CD38 in inflammatory bowel disease. *Biomed Res Int*. 2019;2019:3950628.
49. An P, Menguao J, Megyao J, et al. Protection of 318 inflammatory bowel disease patients from the outbreak and rapid spread of COVID-19 infection in Wuhan, China. *Lancet*. 2020 (In Press).
50. Brenner EJ, Ungaro R, Colombel JF, Kappelman MD.Secure-IBD Database Public Data Update 2020. https://covidibd.org/
51. Han C, Duan C, Zhang S, et al. Clinical characteristics of COVID-19 patients with digestive symptoms in Hubei, China. Am J Gastroenterol. 2020; EPub Ahead of Print.
52. Centers for Disease Control and Prevention. Testing for COVID-19. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html?CDC_AA_refVal=https%3A%2F%2Fwww.cdc.gov%2Fcoronavirus%2F2019-ncov%2Fclinical-criteria.html. Accessed March 18, 2020.
53. Ransford R, Langman M. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut*. 2002;51:536–539.
54. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med*. 2006;3:e343.
55. Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med*. 2018;197:757–767.
56. Ni Y-N, Chen G, Sun J, et al. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23:99.
57. Lee DTS, Wing YK, Leung HCM, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. *Clin Infect Dis*. 2004;39:1247–1249.
58. Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol*. 2004;31:304–309.
59. Xiao JZ, Ma L, Gao J, et al. Glucocorticoid-induced diabetes in severe acute respiratory syndrome: the impact of high dosage and duration of methylprednisolone therapy. *Zhonghua Nei Ke Za Zhi*. 2004;43:179–182.
60. Li Y. Relationship between glucocorticoid receptor and deficiency syndrome and the regulation of traditional Chinese medicine. *Zhong Xi Yi Jie He Xue Bao*. 2004;2:172–174.
61. Tinsley A, Navabi S, Williams ED, et al. Increased risk of influenza and influenza-related complications among 140,480 patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2019;25:369–376.
62. Long MD, Martin C, Sandler RS, Kappelman MD. Increased risk of pneumonia among patients with inflammatory bowel disease. *Am J Gastroenterol*. 2013;108:240–248.
63. Orlicka K, Barnes E, Culver EL. Prevention of infection caused by immunosuppressive drugs in gastroenterology. *Ther Adv Chronic Dis*. 2013;4:167–185.
64. Dorrington AM, Selinger CP, Parkes GC, et al. The historical role and contemporary use of corticosteroids in inflammatory bowel disease. *J Crohns Colitis*. 2020.
65. Sherlock ME, Seow CH, Steinhart AH, Griffiths AM. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2010;10:CD007698.
66. Benchimol EI, Seow CH, Otley AR. Steinhart AH. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2009;1:CD002913.
67. Manguso F, Bennato R, Lombardi G, et al. Efficacy and safety of oral beclomethasone dipropionate in ulcerative colitis: a systematic review and meta-analysis. *PLoS ONE*. 2016;11:e0166455.
68. Van Assche G, Manguso F, Zibellini M, et al. Oral prolonged release beclomethasone dipropionate and prednisone in the treatment of active ulcerative colitis: results from a double-blind, randomized, parallel group study. *Am J Gastroenterol*. 2015;110:708–715.
69. Bonovas S, Nikolopoulos GK, Lytras T, et al. Comparative safety of systemic and low-bioavailability steroids in inflammatory bowel disease: Systematic review and network meta-analysis. *Br J Clin Pharmacol*. 2018;84:239–251.
70. Kirchgesner J, Lemaitre M, Carrat F, et al. Risk of serious and opportunistic infections associated with treatment of inflammatory bowel diseases. *Gastroenterology*. 2018;155:337–46. e10.
71. Seksik P, Cosnes J, Sokol H, et al. Incidence of benign upper respiratory tract infections, HSV and HPV cutaneous infections in inflammatory bowel disease patients treated with azathioprine. *Aliment Pharmacol Ther*. 2009;29:1106–1113.
72. Cheng K-W, Cheng S-C, Chen W-Y, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res*. 2015;115:9–16.
73. Ibrahim A, Ahmed M, Conway R, Carey JJ. Risk of infection with methotrexate therapy in inflammatory diseases: a systematic review and meta-analysis. *J Clin Med*. 2019;8:15.
74. Conway R, Low C, Coughlan RJ, et al. Methotrexate use and risk of lung disease in psoriasis, psoriatic arthritis, and inflammatory bowel disease: systematic literature review and meta-analysis of randomised controlled trials. *BMJ*. 2015;350:h1269.
75. Lichtenstein GR, Feagan BG, Cohen RD, et al. Serious infection and mortality in patients with Crohn's disease: more than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol*. 2012;107:1409–1422.
76. Shah ED, Farida JP, Siegel CA, et al. Risk for overall infection with anti-TNF and anti-integrin agents used in IBD: a systematic review and meta-analysis. *Inflamm Bowel Dis*. 2017;23:570–577.
77. Singh S, Facciorusso A, Dulai PS, et al. Comparative risk of serious infections with biologic and/or immunosuppressive therapy in patients with inflammatory bowel diseases: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol*. 2020;18:69–81. e3
78. Lv S, Han M, Yi R, et al. Anti-TNF-alpha therapy for patients with sepsis: a systematic meta-analysis. *Int J Clin Pract*. 2014;68:520–528.
79. Cheng VC, Lau SK, Woo PC, Yuen KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev*. 2007;20:660–694.
80. Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946–1960.
81. Kalb RE, Fiorentino DF, Lebwohl MG, et al. Risk of serious infection with biologic and systemic treatment of psoriasis: results from the psoriasis longitudinal assessment and registry (PSOLAR). *JAMA Dermatol*. 2015;151:961–969.
82. Hanauer SB, Sandborn WJ, Feagan BG, et al. IM-UNITI: three-year efficacy, safety, and immunogenicity of ustekinumab treatment of Crohn's disease. *J Crohns Colitis*. 2020;14:23–32.
83. Bye WA, Jairath V, Travis SPL. Systematic review: the safety of vedolizumab for the treatment of inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;46:3–15.

84. Mocko P, Kawalec P, Pilc A. Safety profile of biologic drugs in the therapy of Crohn disease: a systematic review and network meta-analysis. *Pharmacol Rep*. 2016;68:1237–1243.
85. Mocko P, Kawalec P, Pilc A. Safety profile of biologic drugs in the therapy of ulcerative colitis: a systematic review and network meta-analysis. *Pharmacotherapy*. 2016;36:870–879.
86. Colombel J-F, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. *Gut*. 2017;66:839–851.
87. Bourges D, Chevaleyre C, Wang C, et al. Differential expression of adhesion molecules and chemokines between nasal and small intestinal mucosae: implications for T- and sIgA+ B-lymphocyte recruitment. *Immunology*. 2007;122:551–561.
88. Van Assche G, Vermeire S, Ballet V, et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. *Gut*. 2012;61:229–234.
89. Winthrop KL, Melmed GY, Vermeire S, et al. Herpes zoster infection in patients with ulcerative colitis receiving tofacitinib. *Inflamm Bowel Dis*. 2018;24:2258–2265.
90. Wollenhaupt J, Lee EB, Curtis JR, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. *Arthritis Res Ther*. 2019;21:89.
91. Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376:1723–1736.
92. Harigai M. Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis. *Rheumatology (Oxford)*. 2019;58(Suppl 1):i34–i42.
93. Weisshof R, Aharoni Golan M, Sossenheimer PH, et al. Real-world experience with tofacitinib in IBD at a Tertiary Center. *Dig Dis Sci*. 2019;64:1945–1951.
94. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020;20:400–402.
95. European Centre for Disease Prevention and Control. Technical Report: Guidance for discharge and ending isolation in the context of widespread community transmission of COVID-19 – first update. https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-guidance-discharge-and-ending-isolation-first%20update.pdf. Accessed April 11, 2020.
96. Ananthakrishnan AN, McGinley EL. Infection-related hospitalizations are associated with increased mortality in patients with inflammatory bowel diseases. *J Crohns Colitis*. 2013;7:107–112.
97. Fong MW, Gao H, Wong JY, et al. Nonpharmaceutical measures for pandemic influenza in nonhealthcare settings-social distancing measures. *Emerg Infect Dis*. 2020;26:976–984.
98. Ahmed F, Zviedrite N, Uzicanin A. Effectiveness of workplace social distancing measures in reducing influenza transmission: a systematic review. *BMC Public Health*. 2018;18:518.
99. Hollander JE, Carr BG. Virtually perfect? Telemedicine for Covid-19. *N Engl J Med*. 2020;382:1679–1681
100. Clare DF, Alexander FC, Mike S, et al. Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol*. 2009;21:71–75.
101. World Health Organisation.A multi-centre, adaptive, randomized, double-blind, placebocontrolled clinical trial of the safety and efficacy of investigational therapeutics for the treatment of COVID-19 in hospitalized patients.2020.
102. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *mBio*. 2018;9.
103. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269–271.
104. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *BioSci Trends*. 2020.
105. Chu CM, Cheng VC, Hung IF, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59:252–256.
106. Chan JF, Yao Y, Yeung ML, et al. Treatment with lopinavir/ritonavir or interferon-beta1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis*. 2015;212:1904–1913.
107. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med*. 2020.
108. Devaux CA, Rolain J-M, Colson P, Raoult D. New insights on the antiviral effects of chloroquine against coronavirus: what to expect for COVID-19? *Int J Antimicrob Agents*. 2020.
109. Colson P, Rolain J-M, Lagier J-C, et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents*. 2020;105932.
110. Colson P, Rolain JM, Raoult D. Chloroquine for the 2019 novel coronavirus SARS-CoV-2. *Int J Antimicrob Agents*. 2020;55:105923.
111. Gautret P, Lagier J-C, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents*. 2020;105949.
112. Li G, De Clercq E. Therapeutic options for the 2019 novel coronavirus (2019-nCoV). *Nat Rev Drug Discov*. 2020;19:149–150.
113. Chang C, Huang J, Cheng Z, et al. Faviiravir versus arbidol for COVID- 19: a randomized clinical trial. [In press]. *medRxiv*. 2020.
114. Chinese Clinical Trials Registry 2020. http://www.chictr.org.cn/searchprojen.aspx?title=COVID-19&officialname=&subjectid=&secondaryid=&applier=&studyleader=&ethicalcommitteesanction=&sponsor=&studyailment=&studyailmentcode=&studytype=0&studystage=0&studydesign=0&minstudyexecutetime=&maxstudyexecutetime=&recruitmentstatus=0&gender=0&agreetosign=&secsponsor=&regno=&regstatus=0&country=&province=&city=&institution=&institutionlevel=&measure=&intercode=&sourceofspends=&createyear=0&isuploadrf=&whetherpublic=&btngo=btn&verifycode=&page=1
115. Schwartz J, King C-C, Yen M-Y.Protecting healthcare workers during the coronavirus disease 2019 (COVID-19) outbreak: lessons from Taiwan's severe acute respiratory syndrome response.Clin Infect Dis. 2020.
116. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062.
117. Phan LT, Maita D, Mortiz DC, et al. Contact and self-contact patterns of healthcare workers: implications for infection prevention and control. *Clin Infect Dis*. 2019;*69*(Supplement_3):S178–S184.
118. Kuenzig ME, Rezaie A, Kaplan GG, et al. Budesonide for the induction and maintenance of remission in Crohn's disease: systematic review and meta-analysis for the Cochrane collaboration. *J Can Assoc Gastroenterol*. 2018;1:159–173.
119. Rizzello F, Gionchetti P, D'Arienzo A, et al. Oral beclometasone dipropionate in the treatment of active ulcerative colitis: a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2002;16(6):1109–1116.
120. Feagan BG, Bhayat F, Khalid M, et al. Respiratory tract infections in patients with inflammatory bowel disease: safety analyses from vedolizumab clinical trials. *J Crohns Colitis*. 2018;12:905–919.
121. Tofacitinib [Internet].Truven Health Analytics. 2020 [cited 14 March 2020]. www.micromedexsolutions.com. Subscription required to view.
122. Tofacitinib [Internet].Truven Health Analytics. 2020 [cited 14 March 2020]. www.micromedexsolutions.com. Subscription required to view.
123. Cohen SB, Tanaka Y, Mariette X, et al. Long-term safety of tofacitinib for the treatment of rheumatoid arthritis up to 8.5 years:

integrated analysis of data from the global clinical trials. *Ann Rheum Dis*. 2017;76:1253–1262.
124. Derijks LJJ, Wong DR, Hommes DW, van Bodegraven AA. Clinical pharmacokinetic and pharmacodynamic considerations in the treatment of inflammatory bowel disease. *Clin Pharmacokinet*. 2018;57:1075–1106.
125. Gisbert JP, Nino P, Cara C, Rodrigo L. Comparative effectiveness of azathioprine in Crohn's disease and ulcerative colitis: prospective, long-term, follow-up study of 394 patients. *Aliment Pharmacol Ther*. 2008;28:228–238.
126. Ben-Horin S, Van Assche G, Chowers Y, et al. Pharmacokinetics and immune reconstitution following discontinuation of thiopurine analogues: implications for drug withdrawal strategies. *J Crohns Colitis*. 2018;12:1410–1417.
127. Vande Casteele N, Baert F, Bian S, et al. subcutaneous absorption contributes to observed interindividual variability in adalimumab serum concentrations in Crohn's disease: a prospective multicentre study. *J Crohns Colitis*. 2019;13:1248–1256.
128. Ternant D, Bejan-Angoulvant T, Passot C, et al. Clinical pharmacokinetics and pharmacodynamics of monoclonal antibodies approved to treat rheumatoid arthritis. *Clin Pharmacokinet*. 2015;54:1107–1123.
129. Klotz U, Teml A, Schwab M. Clinical pharmacokinetics and use of infliximab. *Clin Pharmacokinet*. 2007;48:645–660.
130. Ternant D, Aubourg A, Magdelaine-Beuzelin C, et al. Infliximab pharmacokinetics in inflammatory bowel disease patients. *Ther Drug Monit*. 2008;30:523–529.
131. Hemperly A, Vande CN. Clinical pharmacokinetics and pharmacodynamics of infliximab in the treatment of inflammatory bowel disease. *Clin Pharmacokinet*. 2018;57:929–942.
132. Tian H, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. *Bull NYU Hosp Jt Dis*. 2007;65:168–173.
133. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. *J Acquir Immune Defic Syndr*. 2011;58:385–391.
134. Quetglas EG, Armuzzi A, Wigge S, et al. Review article: the pharmacokinetics and pharmacodynamics of drugs used in inflammatory bowel disease treatment. *Eur J Clin Pharmacol*. 2015;71:773–799.

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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